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Radiation and Alzheimer's Disease (AD)

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Alzheimer's disease (AD) is the most common form of dementia, and accounts for 60 to 80 percent of dementia cases. While about one-third of all people age 85 and older may have Alzheimer's disease, and the number of people with the disease doubles every 5 years beyond age 65, its early onset may start from the ages of 40s and 50s. Old age and genetic factor are two most important factors for the development of Alzheimer's disease. Epidemiological studies have suggested that excessive alcohol consumption, smoking, environmental toxin such as pesticides (Dichlorodiphenyltrichloroethane or DDT), food additives (such as nitrogen-based chemicals which are converted to toxic nitrosamines during cooking), contamination (mussels contaminated with demonic acid), food components (two amino acids in seeds of certain legumes which enhance the action of the neurotransmitter glutamate), air pollution (such as aerosolized nickel nanoparticles, a component of air pollution) may also play important roles in the development of the disease [1]. Serious head injury, heart disease, diabetes, stroke, high blood pressure and high cholesterol which damage the heart and blood vessels may be indirectly related to the development of AD due to the increase of β-amyloid (Aβ).

Recent systematic review of bibliographic databases from PubMed, EMBASE, Cochrane Library and Web of Science suggests that occupational exposure to extremely low frequency magnetic fields (ELF-MF) to welders, electric utility workers, train drivers and sewing machine operators may increase the risk of AD [2,3]. Experimental studies indicated that low-dose radiation exposures (10 cGy) induced genes not affected by high-dose radiation (2 Gy) and that low-dose genes were associated with unique pathways and functions. Nine neural signaling pathways had a high degree of concordance in their transcriptional response in mouse brain tissue after low-dose irradiation, in the aging human brain (unirradiated) and in brain tissue from patients with Alzheimer's disease. Mice exposed to high-dose radiation did not show these effects and associations. It suggests that the molecular response of the mouse brain within a few hours after low-dose irradiation involves the down-regulation of neural pathways associated with cognitive dysfunctions that are also down-regulated in normal human aging and Alzheimer's disease [4,5]. Galactic cosmic radiation consisting of high-energy, high-charged (HZE) particles such as (56) Fe at 100 mGy to 1 Gy reduced cognitive abilities. Acceleration of Aβ plaque pathology was observed in male Amyloid precursor protein (APP)/Presenilin 1 (PS1) mice. Further study suggested that (56) Fe particle-induced alterations in Aβ trafficking through the blood brain barrier might be related to plaque increase leading to AD [6]. Chronic low-dose-rate radiation exposure (1 mGy/day or 20 mGy/day) over 300 days with cumulative doses of 0.3 Gy and 6.0 Gy, respectively induced a marked alteration in the phosphoproteome and an inhibition of cAMP responsive element binding protein (CREB) signalling. Both dose rate irradiations reduced the number of activated microglia in the molecular layer of hippocampus which paralleled with decreased levels of tumor necrosis factor alpha (TNFα) expression. At the lower dose rate of 1mGy/day, alteration of Rac1-Cofilin signalling and lipid peroxidation was induced. The overlap of these changes with those of Alzheimer´s pathology suggests that low dose rate irradiation may be involved in the development of Alzheimer´s disease [7]. In the United States, analysis of AD death rates versus radon background radiation and total background radiation suggested that ionizing radiation was a risk factor for AD. Intranasal inhalation of radon gas could subject the rhinencephalon and hippocampus to damaging radiation that initiated AD [8]. The Alzheimer neurofibrillary tangle is composed of tau, which is one of the most common pathological hallmarks of AD and tau aggregation pathology at Braak stage 1 1 (out of 6 Braak stages) or beyond affects 50% of the population over the age of 45 [9-11]. Our recent review of the effect of the pre- and post-natal irradiation on animal models and human studies indicated many similarities in hippocampal neuropathology, cognitive impairment and relevant molecular mechanisms between Alzheimer's disease and early life radiation exposure-induced neuropsychological disorders [12-16]. It suggests that irradiation of the brain in early human life may set abnormal developmental events into motion that starts from tau aggregation at the ages of 40s and 50s, leading to the development of Alzheimer's Disease at the late stages of human life. At molecular level, pre- or post-natal irradiation induced brain oxidative stress [15], neuroinflammatory response [16,17], capillary loss or impairment of

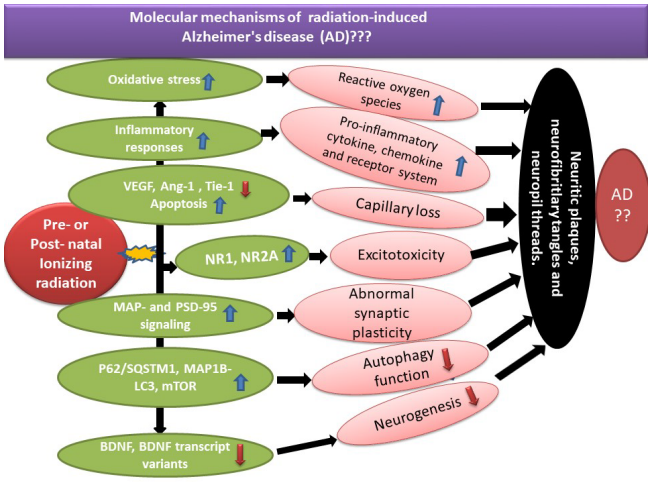

Figure 1: Pre- or post-natal irradiation induced brain oxidative stress, neuroinflammatory response, capillary loss or impairment of angiogenesis, up-regulation of NMDA receptor subunit 1 (NR1) and NR2A, changes of synaptic proteins such as MAP-2 and PSD-95, accumulation of ubiquitin inclusion bodies, autophagosome and down-regulation of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) may induce neuritic plaques, neurofibritlary tangles and neuropil threads leading to the development of alzheimer's disease.

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angiogenesis [18], up-regulation of NMDA receptor subunit 1 (NR1) and NR2A [19], changes of synaptic proteins such as MAP-2 and PSD-95 [20], accumulation of ubiquitin inclusion bodies, autophagosome [21] and down-regulation of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) [22] may induce neuritic plaques, neurofibritlary tangles and neuropil threads leading to the development of Alzheimer's disease (Figure 1).

With increased use of X-ray Computed Tomography (CT scan) for medical diagnosis and radiotherapy, construction of more nuclear power plants worldwide and consequently potential nuclear contamination or accidents, occupational radiation exposure, frequent-flyer risks, manned space exploration and possible radiological terrorism, low dose/dose rate ionizing radiation research becomes much more imperative and urgent nowadays than ever before. Further study with lifetime monitoring of radiation effect of individuals with low dose / low dose rate exposure may still be needed for establishing the close relationship between the radiation exposure and the development of Alzheimer's disease.

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